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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/002,413	01/02/98	ALLEN R	8661-010-999

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EXAMINER	
WILSON, M	
ART UNIT	PAPER NUMBER
1633	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/002,413	Applicant(s) Allen et al.
	Examiner Wilson, Michael C.	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-24* is/are pending in the application.

Of the above, claim(s) *24* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-23* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-24 are pending in the instant application.

The Information Disclosure Statement filed 1-7-99, Paper No. 4, has been considered and made of record.

The revocation of power of attorney filed 12-10-98, Paper No. 5, has been entered and accepted.

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-23, drawn to a method of administering cells to create an immunologically privileged site, classified in class 424, subclass 93.1.

   II. Claim 24, drawn to a method of producing Fas L, classified in class 435, subclass 70.1.

The inventions are distinct, each from the other because of the following reasons: Inventions of Group I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the method of administering cells is used for therapy while the method of producing FasL is used to isolate protein. The reagents and protocols required to create an immunologically privileged site are materially distinct and separate from those used to isolate proteins. The method of creating an

immunologically privileged site is not required to make protein and the method of making protein is not required to create an immunologically privileged site.

These inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and their different classification, and because the search required for Group I is not required for Group II. Therefore, restriction for examination purposes as indicated is proper.

During a telephone conversation with Gladys Monroy on April 1, 1999 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-23. Affirmation of this election must be made by applicant in replying to this Office action. Claim 24 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claims 1-23 are under consideration in the instant application.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for allogenic transplantation for at least 8 months, does not reasonably provide enablement for any transplantation in any animal for any sustained period of time as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The purpose of the specification is to provide an immune privileged site for transplantation of tissue for therapeutic purposes (page 4, line 1). The cells can be allogeneic or xenogeneic (page 7, line 28), transfected with a nucleic acid encoding a therapeutic molecule (page 8, line 25), co-administered with other therapeutic cells (page 3, line 9) or using a matrix (page 12, line 15). Claim 10 is directed toward an allograft, which was known in the art at the time of filing to have some success (Streilein Nov. 17, 1995, Science, Vol. 270, pages 1158-1159; see page. Claim 11 is directed toward a xenograft. At the time of filing, however, it was unpredictable whether xenogeneic transplantation using RPE cells could be obtained. Grisanti et al. (July 1997, Invest. Ophthalmology & Visual Sci., Vol. 38, pages 1619-1626) state immune privilege is not absolute and that histoincompatible tissues can be rejected (page 1619, column 2, 6 lines from the bottom). The immune response of an individual to histoincompatible tissue is caused by the

recognition of surface antigens on the tissue that are recognized by the host immune system as foreign. Without providing an adequate immune privileged site, transplanted xenogeneic tissue would be recognized as histoincompatible and destroyed by the host's immune system. The specification states RPE cells may provide localized immunosuppression as to eliminate the need for systemic immunosuppression or may be used in combination with a systemic immunosuppressant to prevent rejection (paragraph bridging pages 7 and 8). The specification demonstrates isolating and culturing fetal RPE *in vitro* (pages 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE (pages 21-27). The specification does not provide adequate guidance, correlate allogeneic transplantation to xenogeneic transplantation or demonstrate xenogeneic transplantation such that one of skill could obtain an immune privileged site supporting xenogeneic transplantation. While the specification discusses the possibilities of xenogeneic transplantation, the specification does not overcome the unpredictability in preventing the host's immune system from preventing rejection of the histoincompatible tissue. It would require one of skill undue experimentation to use RPE cells for xenogeneic transplantation such that an immune privileged site was created and the histoincompatible tissue would not be destroyed by the host immune system.

Furthermore, at the time of filing, Zhang et al. (May 1998, Invest. Ophthalmology & Visual Sci., Vol. 39, pages 1021-1027) states animal models for RPE transplantation open the door for transplantation in humans; however, the immune reject in humans is unpredictable because humans have a more heterogeneous genetic makeup than strains of laboratory animals

(page 1021, column 2, line 13). In fact, human RPE cells transplants have caused persistent macular edema indicating an immune response, compromising the vision of the patient (sentence bridging pages 1021-1022). This may be due to the breakdown of the microenvironment of the retina caused by retinal degeneration (page 1026, sentence bridging columns 1 and 2) or by the procedure of transplantation. The specification does not provide any guidance how to maintain an immune privileged site in any tissue in humans such that a therapeutic effect in any disease can be obtained.

Finally, the state of the art was such that transplantations of allogeneic tissue were rejected by at least 8 months (Ye et al., 1993, Current Eye research, Vol. 12, pages 629-639). The specification does not overcome the unpredictability in obtaining an immune privileged site for allogeneic tissue for more than 8 months because applicants do not provide adequate guidance how to prevent an immune response against the transplanted tissue or how to obtain greater immune privilege. It would require one of skill undue experimentation to determine how to obtain immune privilege for more than 8 months.

Therefore, in view of the lack of guidance in the specification regarding how to create an immune privileged site in any tissue in any animal using xenogeneic or allogeneic transplants as broadly claimed, the lack of correlation between the , the state of the art, the examples provided and the breadth of the claims, the ordinary artisan at the time of the instant invention would not have known how to make and/or use the claimed invention with a reasonable expectation of success.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-7, 9-16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "growth factor, cytokine, ... angiogenic factor" in claims 4 and 19 is indefinite. The phrase is an improper Markush group because a number of the molecules listed are growth factors, interleukins are cytokines, a number of the molecules listed are inhibitors of cytokines, peptide growth and CSF is a differentiation factor. In addition, the "or" on line 3 of claim 4 is unclear. Applicants are requested to clarify the intended claimed subject matter.

Claims 6 and 15 recite the limitation "co-administered cells" in 1, 2 or 3. There is insufficient antecedent basis for this limitation in claim 1 and 2.

In claim 3, the phrase "cells that supply ..." on line 5 is indefinite because it is unclear whether the cells are RPE of line 4 or the cells of line 3.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-2, 4, 7, 9, 12, 13, 16, 19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Ye et al. (1993, Current Eye research, Vol. 12, pages 629-639).

Ye et al. teach treating retinal degeneration by administering $2.1x10^4$ allogeneic RPE cell transplants to the retina of rabbits wherein the immunologic privilege occurs and the number of RPE cells increases in the retina (see especially page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and page 631, column 2, line 20). Retinal degeneration is considered to be a neurological disorder (claim 13) because RPE cells are paraneural cells. Transplanted RPE cells can be detected for up to 8 months (page 631, column 2, last full paragraph). RPE cells inherently secrete FasL and cytokines which are biologically active molecules as in claim 4. Therefore, Ye et al. anticipate all the limitations of the claims.

Claims 1, 2-4, 6, 7, 9, 10, 12, 13, 16-21 and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by Cherksey (U.S. Patent 5,618,531, April 8, 1997).

Cherksey teach treating Parkinson's disease using $300\text{-}3.75x10^5$ RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). Parkinsons' disease is considered to be a neurological disorder (claim 13). The RPE cells can be co-administered with glial cells (column 9, line 2). RPE cells secrete dopamine (column 8, line

40) which is a neurotransmitter (claim 4) or chemokine (claims 4 and 19). RPE cells inherently secrete FasL and create an immunologically privileged site. Thus, Cherksey anticipate all the limitations of the claims.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997).

Cherksey teach treating Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). RPE cells inherently secrete FasL and create an immunologically privileged site. Cherksey does not teach re-administering cells. However, at the time of filing, it would have been obvious to re-administer cells because it was common practice for the ordinary artisan to repeat treatments to obtain therapeutic effects. One of ordinary skill would have had a reasonable expectation of success in treating Parkinson's disease by re-administering RPE cells.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-3, 5, 7, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) in view of Goldstein et al. (U.S. Patent 5,300,436, April 5, 1994).

Cherksey teach treating Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). RPE cells inherently secrete FasL and create an immunologically privileged site. Cherksey does not teach transfecting cells with nucleic acids encoding a protein or other molecule.

However, at the time of filing, Goldstein et al. teach treating Parkinson's by transfecting cells with DNA encoding tyrosine hydroxylase (column 4, line 50) and transplantation in the brain in the amount of 1-10^3 to about 1x10^7 (column 17, line 49). Goldstein et al. also teach the cells can be xenogeneic (column 17, line 41).

Thus, it would have been obvious to use the method of treating Parkinson's using RPE cells by Cherksey and transfect the cells with tyrosine hydroxylase taught by Goldstein et al. Motivation is provided by Goldstein et al. by stating the RPE cells can be used to transfect with tyrosine hydroxylase (column 15, lines 26-61, see line 59). One of ordinary skill would have had a reasonable expectation of success in obtaining a treatment for Parkinsons's disease using

allogeneic RPE cells transfected with tyrosine hydroxylase for at least 8 months and with xenogeneic cells for at least some sustained period of time.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) in view of Selawry et al. (1993, Cell Transplantation, Vol. 2, pages 123-129) and Streinlein (Nov. 17, 1995, Science, Vol. 270, pages 1158-1159).

Cherksey teach treating Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). RPE cells inherently secrete FasL and create an immunologically privileged site. Cherksey does not teach a kit with RPE cells and pancreatic islet of Langerhans cells.

However, at the time of filing, Selawry teach administering pancreatic islet of Langerhans cells with Sartoli cells that produce an immune privileged site for 201 days in rats to prevent hyperglycemia (page 125, column 2, last paragraph).

Thus, it would have been obvious to administer pancreatic islet of Langerhans cells with RPE cells which also produce an immune privileged site to prevent hyperglycemia. Motivation to combine the references is provided by Streinlein by stating RPE cells and Sartoli cells can both be used to create immune privileged sites because they both secrete FasL (page 1158, column 2, first

full paragraph). One of ordinary skill would have had a reasonable expectation of success obtaining an immunologically privileged site and preventing hyperglycemia using RPE cells and pancreatic islet of Langerhans cells.

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, can be reached on (703) 308-2801. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson
April 12, 1999

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630